nonionic surfactant. New claims 57-65 are product-by-process claims requiring the presence of a non-lipid surfactant. Support may be found on page 4, line 23 to page 5, line 16. New claims 66-81 require the presence of a non-lipid surfactant at a specified amount. Support may be found on page 4, line 23 to page 5, line 16 and page 10, line 19 to page 11, line 16. No new matter has been added. New claims 67 and 72-81 require the presence of a bioactive agent. Support for bioactive agents may be found on page 13, lines 6-12.

A total of 38 claims including 5 independent claims will be pending upon entry of this amendment. No fee is believed to be due since 57 total and 11 independent claims were paid for upon the filing of the subject continuation application on July 24, 1998. However, if any additional fee is required, please charge the required fee to Fulbright & Jaworski LLP Deposit Account No. 50-1212/10024052/SLH.

REJECTION UNDER 35 U.S.C. § 102

The Examiner rejected claims 1, 52, 53 and 56 under 35 U.S.C. §§ 102(b) and 102(e) as anticipated by Mehta et al., U.S. Patent No. 4,950,432 (the '432 patent) and Mehta et al., U.S. Patent No. 5,811,119 (the '119 patent), respectively (collectively "*Mehta*"). The Examiner asserted that *Mehta* anticipates the claimed invention by disclosure of preliposomal powders containing a drug and a mixture of phospholipids because " . . . applicant has not shown that the instant preliposomal powders are patentably distinct from the preliposomal powder of Mehta; applicant provides no experimental evidence to that effect." October 23, 2001 Office action at page 2.

In response, Applicants respectfully disagree. However, in order to advance prosecution and without conceding the correctness of this rejection, Applicants have amended the claims to recite that "non-lipid surfactant" is included in the lyophilates of the invention.

It is axiomatic that for a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, it has to meet every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991) ("Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference.").

In this case, all pending claims, including the amended and new claims, now recite that a "non-lipid surfactant" is a necessary ingredient of a lyophilate of the invention. *Mehta* does not disclose or suggest such a requirement, as noted by the Examiner on page 3, last sentence, of the October 23, 2001 Office action. Therefore, *Mehta* is missing at least one element recited in all pending claims.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 102 have been obviated or overcome. Accordingly, the Examiner is respectfully requested to reconsider and withdraw these rejections.

REJECTION UNDER 35 U.S.C. § 103

The Examiner asserted that the remaining claims, *i.e.* claims 2-9 and 54-55, are allegedly obvious under 35 U.S.C. § 103 over *Mehta* (*i.e.*, the '432 or '119 patent cited above) in view of Unger et al., U.S. Patent No. 5,585,112 ("*Unger*"), Isliker et al, U.S. Patent No. 5,089,602 ("*Isliker*") or Hsu, U.S. Patent No. 5,653,996 ("*Hsu*"), individually or in combination.

In response, Applicants respectfully disagree.

The objective standard for obviousness under 35 U.S.C. § 103 as set forth by the Supreme Court of the United States in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966) requires the Examiner to ascertain: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art;

and (4) objective evidence of non-obviousness, if any. The Federal Circuit has also held that the prior art must either expressly disclose every claim limitation or suggest modifications to meet every claim limitation. *Litton Indus. Products, Inc. v. Solid State Systems*, 755 F.2d 158, 164 (Fed. Cir. 1985).

The Federal Circuit has made it clear that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). It is improper to take a single line in a reference out of context and rely upon it with the benefit of hindsight to show obviousness in a complex multi-step process never before disclosed or suggested. "[E]ach prior art reference must be evaluated as an entirety, and all of the prior art must be evaluated as a whole." *Panduit v. Dennison Mfg. Co.*, 227 U.S.P.Q. 337, 344 (Fed. Cir. 1985).

The Federal Circuit also requires that the Office identify a sufficient motivation to combine references. In *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 57 U.S.P.Q.2d 1611 (Fed. Cir. 2000), the court emphasized that sufficient reasoning is required regarding what would have motivated the skilled artisan to select the cited references and combine them to render the claimed invention obvious. *Ruiz, Id.*, citing with approval, *In re Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine."). Moreover, the reasoning for combinability must be clear and particular. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1348-49, 53 U.S.P.Q.2d 1580, 1586-87 (Fed. Cir. 2000) ("Although a reference need not expressly teach that the disclosure contained therein should be combined with another, combinability, in whatever form, must nevertheless be 'clear and particular'.") (upholding validity of claims for lack of suggestion to combine asserted references) (quoting *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

Mehta was discussed above. Briefly, *Mehta* discloses lyophilates containing polyene antifungals (the '432 patent) or carotenoids (the '119 patent). As noted by the Examiner, *Mehta* does not disclose the use of a non-ionic surfactant such as Tween in a preliposome-lyophilate. Nor does *Mehta* teach the advantage of fast and convenient reconstitution of liposomes having a relatively small diameter upon addition of aqueous solution.

Unger discloses a method of preparing gas and gaseous precursor-filled microspheres or liposomes (*see* title). The gas-filled liposomes of *Unger* are prepared by a specific gas instillation method (*see* abstract and drawings). Such gas-filled liposomes are extremely large (*e.g.*, 8-60 μm, c. 41, ll. 62-67; 5-25 μm, c. 42, ll. 26-32; 20-60 μm, c. 42, ll. 54-58; 8-10 μm, c. 45, ll. 24-28 and FIGS. 5 and 6). By contrast, reconstitution of the lyophilate of the invention produces liposomes of less than 400 nm average diameter. This size disparity alone teaches away from combining *Unger* with any other reference to arrive at the invention, not to mention the very different purpose of *Unger* in teaching gas-filled liposomes. *Unger* purports to be a complete solution to the problem of preparation of temperature activated gaseous precursor-filled liposomes (abstract, c. 4, ll.1-5) having surprising "echogenicity" and suitable for ultrasound imaging (c. 4, ll. 15-34). *Unger* does not disclose or suggest that its teachings be combined with *Mehta*. *Unger* discloses Tween among a long list of emulsifiers for use as an aid to "maintain[ing] the stability of the gaseous precursor-filled liposomes" (c. 25, ll. 38-48) and not for use with any other liposome (let alone a lyophilate of pre-liposomal materials). The *Unger*

disclosure is very specific in its description of large gaseous liposomes useful for imaging. Nowhere does *Unger* teach or suggest a non-ionic detergent such as Tween for preliposome-lyophilate production, wherein said lyophilate reconstitutes into nanometer-sized liposomes. The Examiner is respectfully invited to explain how use of an emulsifier such as Tween as taught by *Unger* to make large, many micron-sized, gas-filled liposomes can possibly teach or suggest the claimed invention, when combined with either cited *Mehta* patent or any other reference, in view of the fact that the preliposome-lyophilate of the invention reconstitutes into liposomes of 400 nm or less average diameter. *See Ruiz, Id.*

Isliker discloses a process for the manufacture of apolipoproteins from human blood plasma or serum (*see* title). The disclosure of *Isliker* is therefore not even directed to a liposomal preparation, but to apolipoprotein preparation. At the outset, this important distinction argues against combinability with another reference to arrive at the claimed lyophilates. The process for preparing apolipoproteins by *Isliker* was designed to be a much simpler method for apolipoprotein preparation, compared with traditional methods for isolating LDL- and HDL-apolipoproteins (*see* background and c. 3, ll. 14-19). *Isliker* teaches use of the apolipoproteins produced for prophylaxis and therapy of cardiovascular diseases (c. 5, ll. 45-50). The importance of *Isliker* rests on the teaching that apolipoproteins may now be recovered from a previously useless waste product (c. 5, ll. 40-44). Tween is disclosed in *Isliker* as one among a number of "surface active substances" which may replace chaotropic agents used in the preparation of apolipoproteins (c. 3, ll. 42-56). Liposomes are mentioned by *Isliker* in passing as "proteoliposomes which contain apolipoproteins" prepared by the *Isliker* process (c. 5, ll. 4-16). Tween is also disclosed in Example 11 as an alternate surface-active substance for use in that specific apolipoprotein preparation protocol (c. 8, l. 53). *Isliker* purports to be a complete solution to the problem of apolipoprotein preparation from waste products. Nowhere does *Isliker* disclose or suggest that its teaching can be combined with any other reference to arrive at the

claimed lyophilate which reconstitutes into liposomes having an average diameter of 400 nm or less.

Hsu discloses a method for preparing liposomes using aerosolization through a frequency-generated vibrating nozzle (*see* abstract). The advantage as taught by *Hsu* is the use of an ultrasonic atomization nozzle for production of a lipid spray which forms liposomes on a large scale (c. 4, ll. 7-18, 41-45 & 53-57). Nozzle selection is made from a variety of commercially available nozzles to produce flow and particle size according to the desired results (c. 10, ll. 3-57). The teaching of *Hsu* is the production of liposomes by an novel spray technique not requiring added pressurization (c. 8, l. 65 to c. 9, l. 6 and claim 1). Prior art atomization was performed under pressure and was apparently inefficient compared to the *Hsu* method (c. 2, ll. 17-21). A number of surfactants are disclosed as suitable bilayer forming materials, including Tween (c. 5, ll. 26-47). The *Hsu* liposomes are believed to form instantaneously upon spraying (c. 8, l. 43 to c. 9, l. 15). *Hsu* incidentally discloses lyophilization of liposomes, but not preliposomal solutions, as well-known methods of storage and analysis (FIG. 1, c. 12, ll. 37-47 & c. 17, l. 22 to c. 18, l. 60). The *Hsu* method is exemplified by production of liposomes containing a lung surfactant protein known as SP-C (c. 15, l. 55 to c.17, l. 22). Nowhere does *Hsu* disclose or suggest that its teaching can be combined with any other reference to arrive at the claimed preliposomal lyophilate which is not in liposomal form at the time of lyophilization, and which reconstitutes into liposomes having an average diameter of 400 nm or less.

None of the cited combinations disclose or suggest all of the elements recited in the amended claims. Accordingly, the cited references cannot render obvious the claimed invention. Moreover, assuming *arguendo* that at least one cited combination provided all recited claim elements, the Examiner has not provided sufficient reasoning for any combination of the cited references. In fact, the references themselves teach away from their combinability due to their disparate purposes and subject matter.

In view of the foregoing, Applicants submit that all rejections under 35 U.S.C. § 103 have been obviated or overcome. Accordingly, the Examiner is respectfully requested to reconsider and withdraw them.

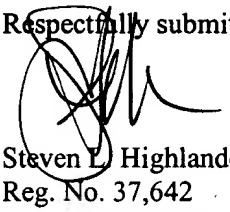
DECLARATION

Further in support of patentability of the claimed invention, Applicants are submitting herewith a Declaration of Roman Perez-Soler Under 37 C.F.R. § 1.132 (the "Declaration"). Dr. Perez-Soler is a co-inventor of the subject matter claimed herein and a skilled artisan eminently qualified to evaluate the cited art discussed above, as is clearly evidenced by his *Curriculum Vitae* attached to the Declaration as Exhibit A. The Examiner is respectfully requested to consider and make of record this additional evidence for patentability.

CONCLUSION

Reconsideration and expedient allowance of all pending claims are earnestly sought. If any issues remain in connection herewith, the Examiner is encouraged to telephone the undersigned to discuss same.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

Date: April 22, 2002

APPENDIX A: MARKED UP COPY OF CLAIMS

1. **(Amended)** A submicron-reconstitute preliposome-lyophilate comprising a non-lipid surfactant.

3. **(Amended)** The submicron-reconstitute preliposome-lyophilate of [claim 2] claim 1 wherein said surfactant is anionic, cationic or nonionic.

8. **(Amended)** The submicron-reconstitute preliposome-lyophilate of [claim 2] claim 3 wherein said surfactant comprises from about 5 mole % to about 0.1 mole % of the lipid content of the submicron-reconstitute preliposome-lyophilate.

53. **(Amended)** A preliposome-lyophilate [constituting liposomes of submicron size (diameter) distribution upon reconstitution into liposomes in the presence of aqueous solution] comprising a non-lipid surfactant and capable of forming liposomes having an average diameter of less than 400 nm when reconstituted in aqueous solution.

54. **(Amended)** The preliposome-lyophilate of claim 53 [comprising a non-lipid surfactant] wherein said surfactant is nonionic.

55. **(Amended)** The preliposome-lyophilate of claim 54 wherein said [non-lipid] nonionic surfactant is selected from the group consisting of polyoxyethylene sorbitan monolaurate having a molecular weight of approximately 1300 and polyoxyethylene sorbitan monooleate having a molecular weight of approximately 1350.

56. **(Amended)** A non-aqueous material [that will form liposomes upon addition of aqueous solution wherein said liposomes constitute submicron size (diameter) distribution upon

reconstitution into liposomes in the presence of aqueous solution] comprising a non-lipid surfactant and capable of forming liposomes upon addition of aqueous solution, wherein said liposomes have an average diameter of less than 400 nm.

57. **(New)** A submicron-reconstitute preliposome-lyophilate product produced by a process comprising:

(a) preparing a solution comprising at least one lipid dissolved in an aqueous/t-butanol solvent system and a non-lipid surfactant, wherein said solution does not contain liposomes at the time of lyophilization; and

(b) lyophilizing said solution to form a submicron-reconstitute preliposome-lyophilate.

58. **(New)** The product of claim 57 wherein said surfactant is anionic, cationic or nonionic.

59. **(New)** The product of claim 58 wherein said surfactant is nonionic.

60. **(New)** The product of claim 59 wherein said surfactant is a Tween surfactant.

61. **(New)** The product of claim 60 wherein said surfactant is Tween 20.

62. **(New)** The product of claim 60 wherein said surfactant is Tween 80.

63. **(New)** The product of claim 61 or claim 62 wherein said surfactant comprises from about 4 mole % to about 2 mole % of the lipid content of the lyophilate.

64. **(New)** The product of claim 58 wherein said surfactant comprises from about 5 mole % to about 0.1 mole % of the lipid content of the lyophilate.

65. **(New)** The product of claim 64 wherein said surfactant comprises from about 4 mole % to about 2 mole % of the lipid content of the lyophilate.

66. **(New)** A lyophilate comprising at least one lipid and a non-lipid surfactant of about 4 mole % or less of lipid content, wherein the lyophilate is capable of forming liposomes in about one minute with hand-shaking upon addition of aqueous solution, which liposomes have an average diameter of less than 400 nm.

67. **(New)** The lyophilate of claim 66 further comprising a bioactive agent.

68. **(New)** The lyophilate of claim 66 wherein said surfactant is nonionic.

69. **(New)** The lyophilate of claim 68 wherein said surfactant is a Tween surfactant.

70. **(New)** The lyophilate of claim 69 wherein said surfactant is Tween 20.

71. **(New)** The lyophilate of claim 69 wherein said surfactant is Tween 80.

72. **(New)** The lyophilate of claim 67 wherein the bioactive agent is selected from the group consisting of an antifungal agent, an antineoplastic agent, an antibiotic, an adjuvant, a vaccine, a contrast agent, a diagnostic agent, a drug targeting agent and a genetic fragment.

73. **(New)** The lyophilate of claim 72 wherein the bioactive agent is an antifungal agent.

74. **(New)** The lyophilate of claim 72 wherein the bioactive agent is an antineoplastic agent.

75. **(New)** The lyophilate of claim 72 wherein the bioactive agent is an antibiotic.

76. **(New)** The lyophilate of claim 72 wherein the bioactive agent is an adjuvant.

77. **(New)** The lyophilate of claim 72 wherein the bioactive agent is a vaccine.

78. **(New)** The lyophilate of claim 72 wherein the bioactive agent is a contrast agent.

79. **(New)** The lyophilate of claim 72 wherein the bioactive agent is a diagnostic agent.

80. **(New)** The lyophilate of claim 72 wherein the bioactive agent is a drug targeting agent.

81. **(New)** The lyophilate of claim 72 wherein the bioactive agent is a genetic fragment.